

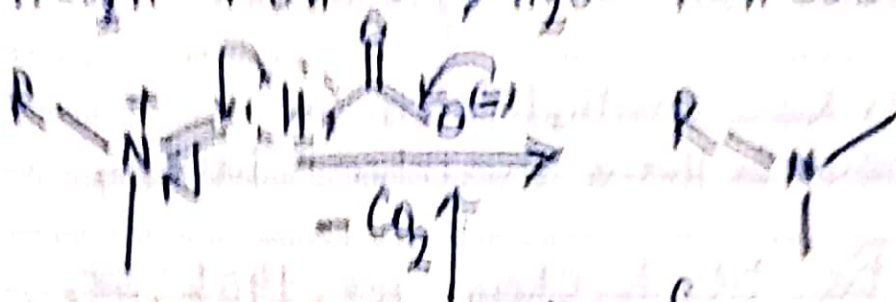
Practice like you've never won. Play like you've never lost. - Michael Jordan

06

Friday

Mar 30/20

Week 10 (688-900)



The second step, i.e., formation of 3° amine is slower due to formation of the iminium ion being somewhat less facile. The reaction does not proceed to the quaternary ammonium stage because the corresponding 3° amine cannot generate the iminium ion.

Chiral amines retain their stereochemistry under the reaction conditions.

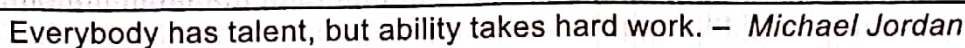
(Farkas, E. & Sunmann, C. T. J. Org. Chem. 1985, 50, 1110-1112)

The Eschweiler-Clarke methylation may even be achieved by using a mixture of paraformaldehyde and oxalic acid dihydrate at a temperature of 100°C.

This process does not require organic solvents or formalin. The latter is generated in situ by thermal/acid catalyzed decomposition of paraform. Oxalic acid can itself act

NOTES

as the hydride donor or get decomposed to HCO_2H which, in turn, acts as the hydride donor.



09

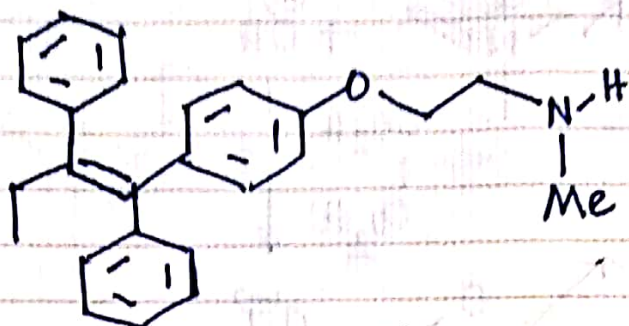
Monday

Mar 2020 Week-11 (069-297)

March

2020

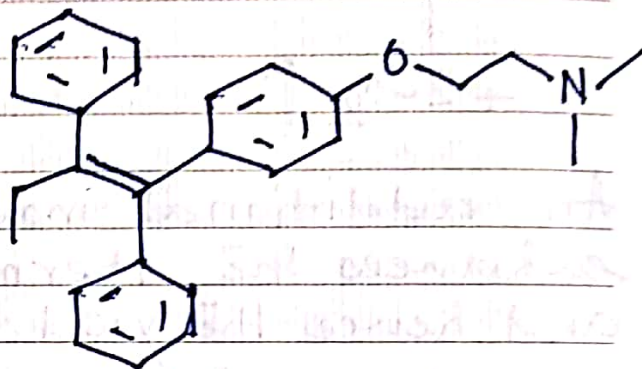
S	M	T	W	T	F	S	S	M	T	W	T	F	S
							1	2	3	4	5	6	7
8	9	10	11	12	13	14	15	16	17	18	19	20	21
22	23	24	25	26	27	28	29	30	31	•	•	•	•



HCHO/HCO₂H, DMSO
↓ Microwave

Desmethyl tamoxifen

Harding, I.R., Jones, I.R.,
Lu, S. Y. & Wood, R.
Tetrahedron Letters 2002,
43, 9487-9488.



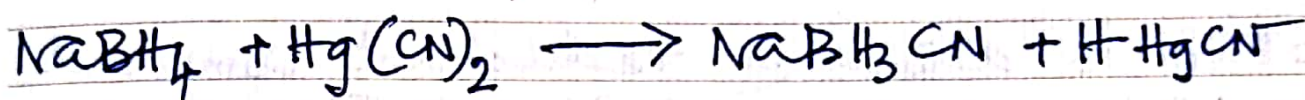
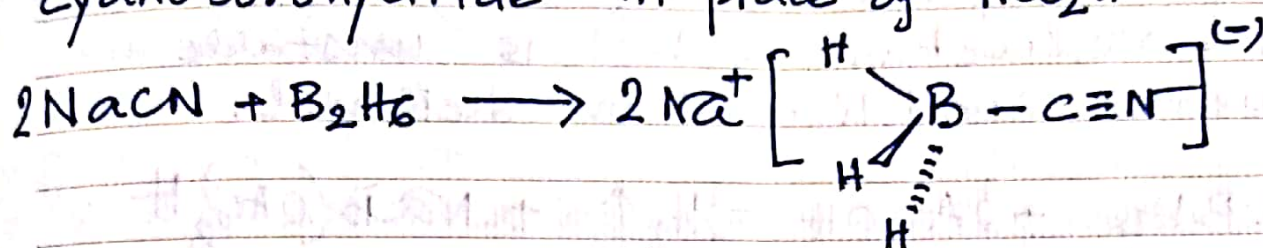
Tamoxifen-d₃.
(Anticancer drug)

Note: The Eschweiler Clarke methylation, resembles the Leuckart-Wallach synthesis of amines; There formamide is employed in place of the 1° or 2° amine.

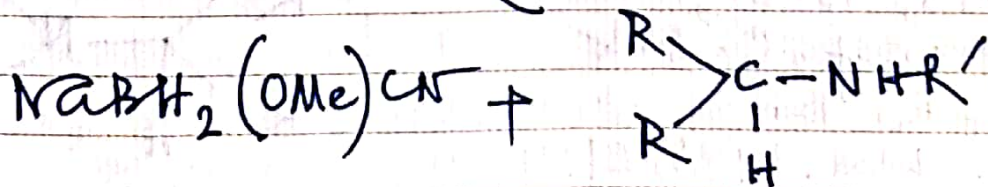
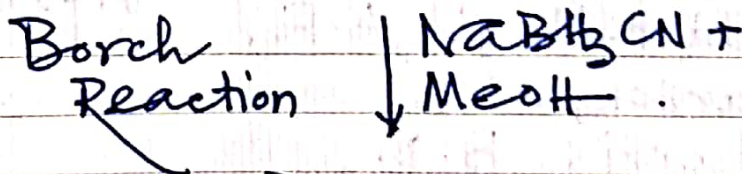
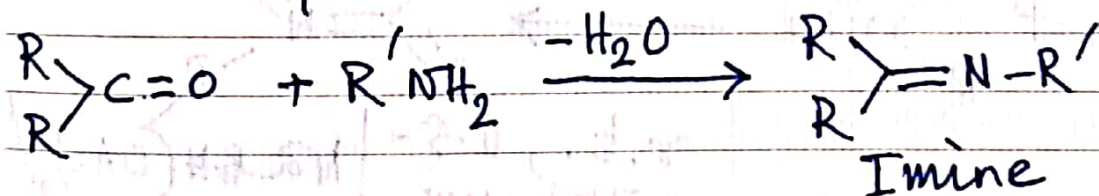
(Elliot, A. & Wildman R.B. J. Am. Chem. Soc. 1948, 70, 1187-1189).

NOTES

A modification of the Eschweiler-Clarke methylation process uses sodium cyanoborohydride in place of HCO_2H .



Sodium cyanoborohydride tolerates aqueous conditions; the presence of cyanide moiety renders this molecule a much weaker hydride donor compared to NaBH_4 and is typically used in reductive amination reactions to transform imines to amines.



(Borch, F.R., Bernstein, M.D. & Durst, NOTES

H.D. J. Am. Chem. Soc. 1971, 93:12, 2897-2904)

11

Wednesday

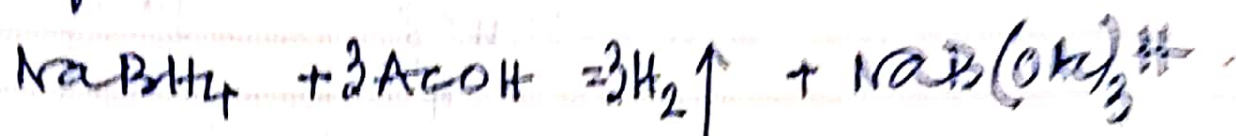
Mar 2020 Week: 11 (071-295)

DATE: / /

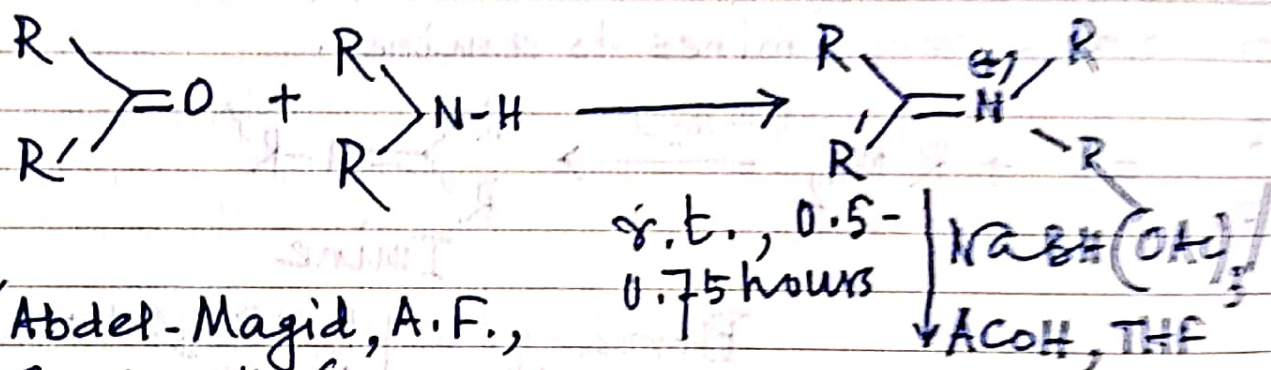
PAGE: /

TIME: /

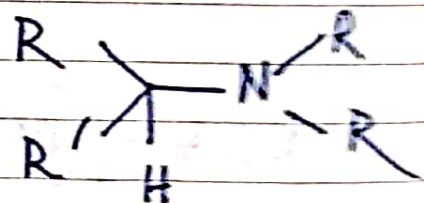
Sodium triacetoxyborohydride or sodium triacetoxyhydroborate (STAB) is another mild reductant but it is unstable in aqueous conditions or in methanol.



STAB is a weaker reductant compared to NaBH_4 or even NaBH_3CN . It can reduce aldehydes but not ketones in general. In presence of AcOH , it is typically employed for the reductive amination of carbonyl compounds.



(Abdel-Magid, A.F.,
Carson, K.G.,
Harris, B.D.,
Maryanof, C.A. &
Shah, R.D.
J. Org. Chem. 1996, 61:11,



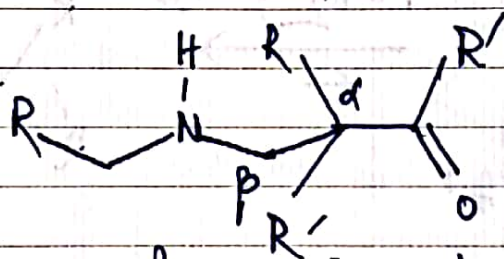
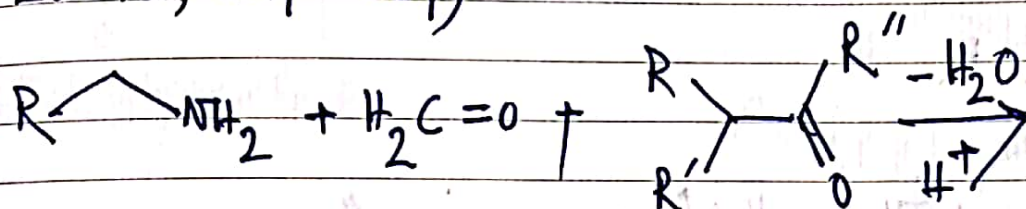
NOTES 3849-3862.

Pandit, C.R. & Mani, N.S.
Synthesis 2009, 23, 4032-4036

Mannich Reaction:

The Mannich reaction essentially consists of amino alkylation of an acidic proton by a carbonyl compound (often formaldehyde) and a 1° or 2° amine or ammoniac. If the acidic proton is α to a carbonyl function, the product is a β -aminocarbonyl compound (Mannich Base).

(Mannich, C. & Krösche, W. Archiv der Pharmazie 1912, 250:1, 647-667).



β -aminocarbonyl compound

3° amines cannot undergo Mannich reaction; they cannot generate the intermediate enamine due to absence of the $>N-H$ proton. The acidic proton may be an α -H with respect to a carbonyl, nitrile, yne, nitro functions. Aromatic, benzylic or even α -imine protons participate in Mannich Reaction. Heterocyclic aromatic compounds, eg. furan, pyrrole, Thiophen, indole, etc. often act as Mannich donor.

NOTES

13

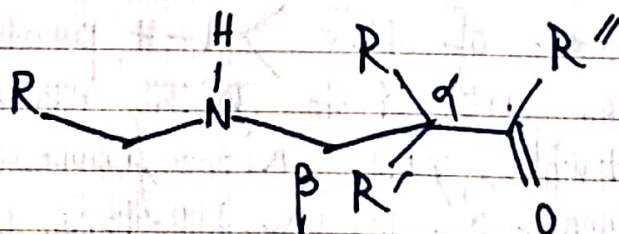
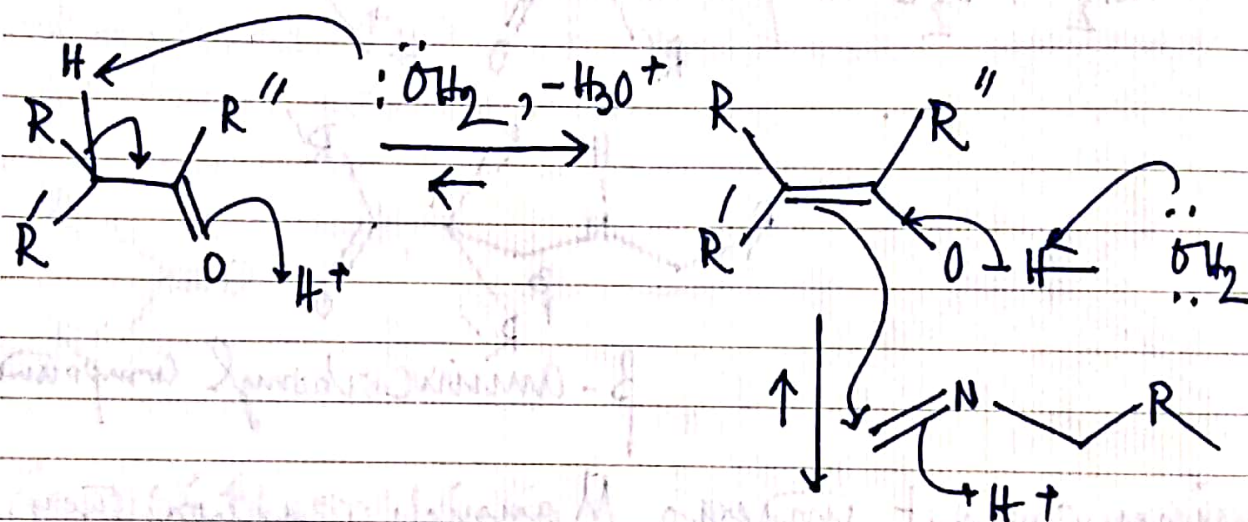
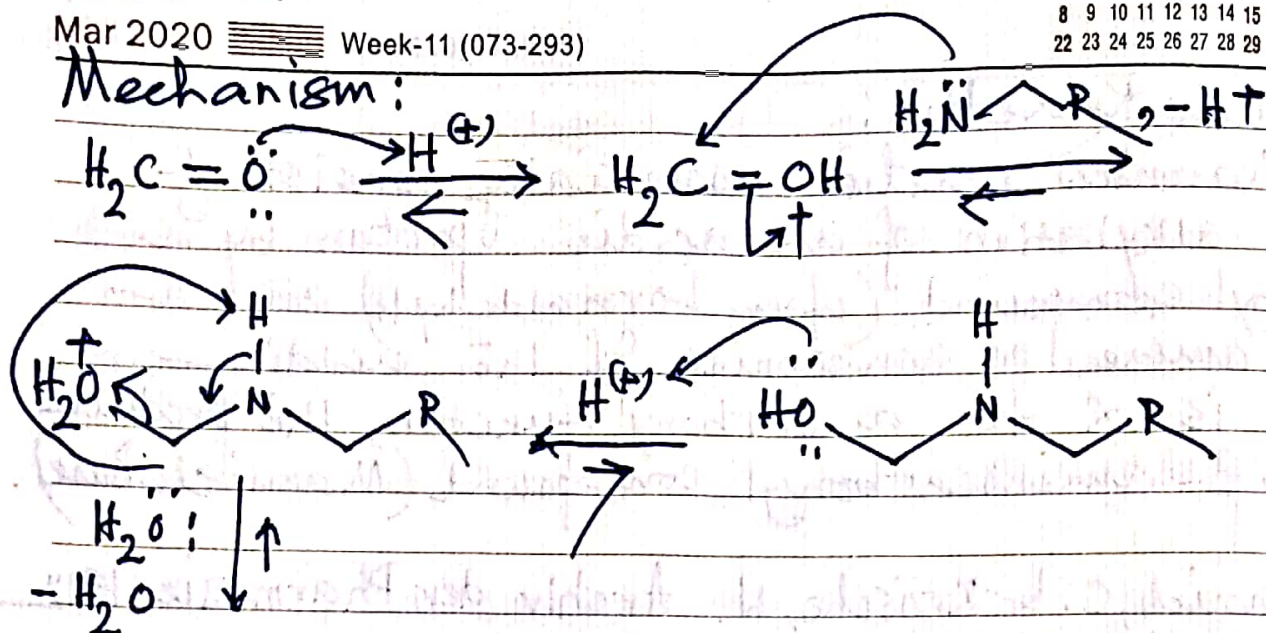
Friday

Mar 2020  Week-11 (073-293)

March

S	M	T	W	T	F	S	S	M	T	W	T	F	S
						1	2	3	4	5	6	7	
8	9	10	11	12	13	14	15	16	17	18	19	20	21
22	23	24	25	26	27	28	29	30	31	...	...	...	...

Mechanism:

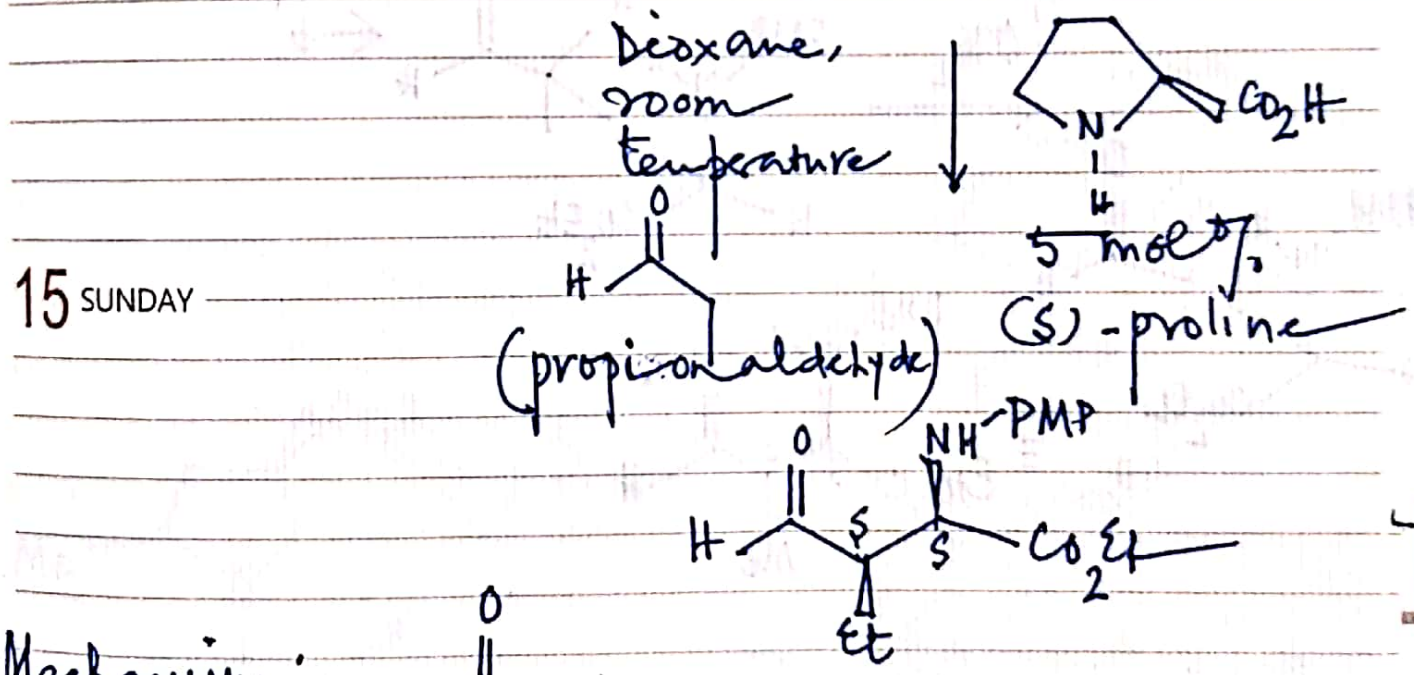
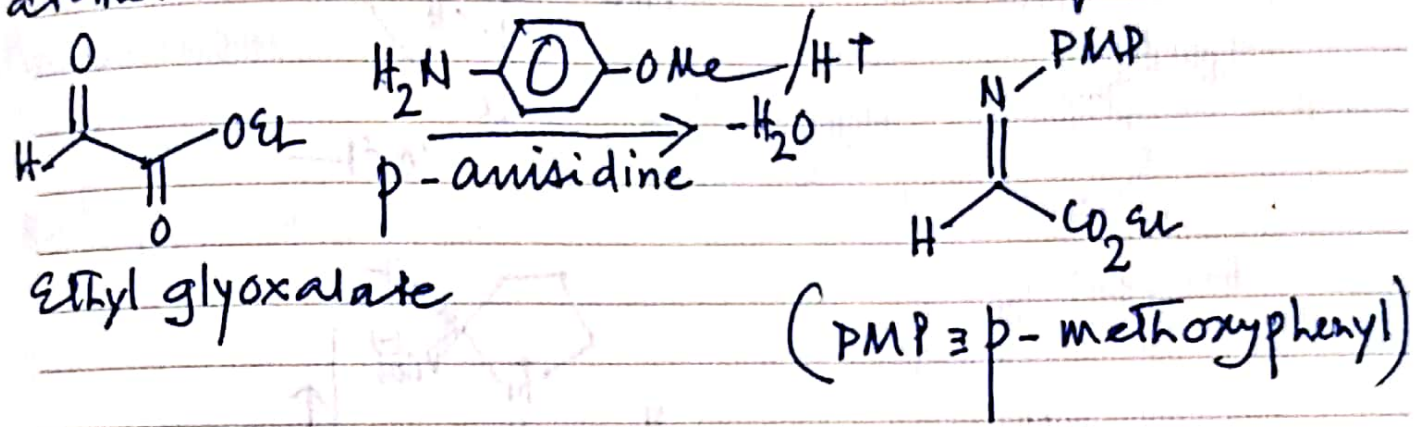


NOTES

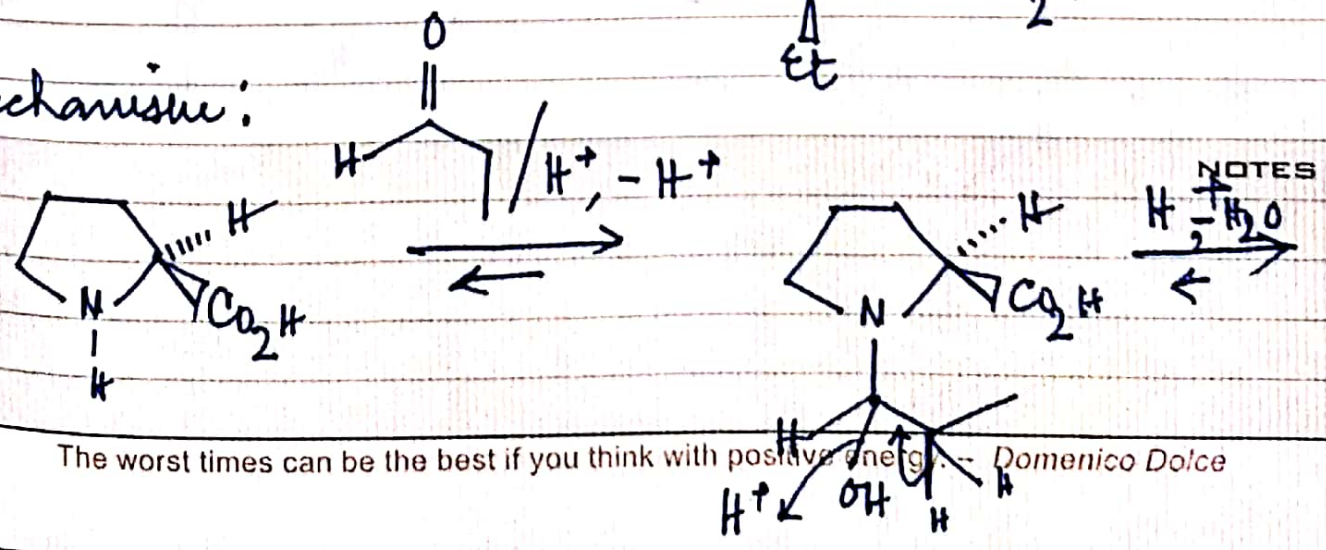
Chirality is generated on the αC , in these cases both enantiomers are formed. The βC is a prochiral centre.

Asymmetric Mannich Reactions:

By employing a chiral catalyst, Mannich reactions can be carried out in an asymmetric manner by exercising chiral control on the α & β carbon atoms.



Mechanism:



16

Monday

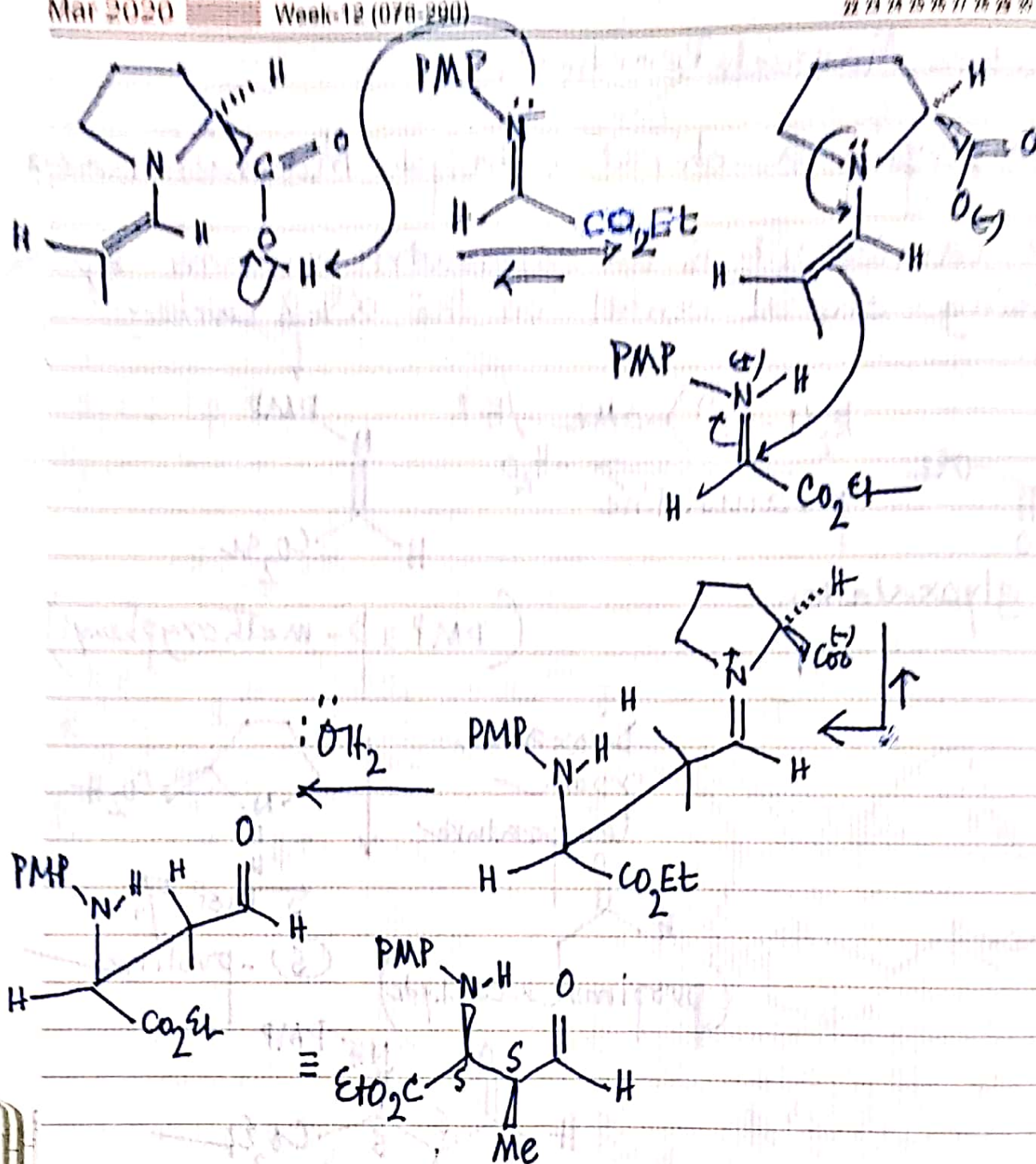
Mar 2020

Week: 12 (070-290)

March

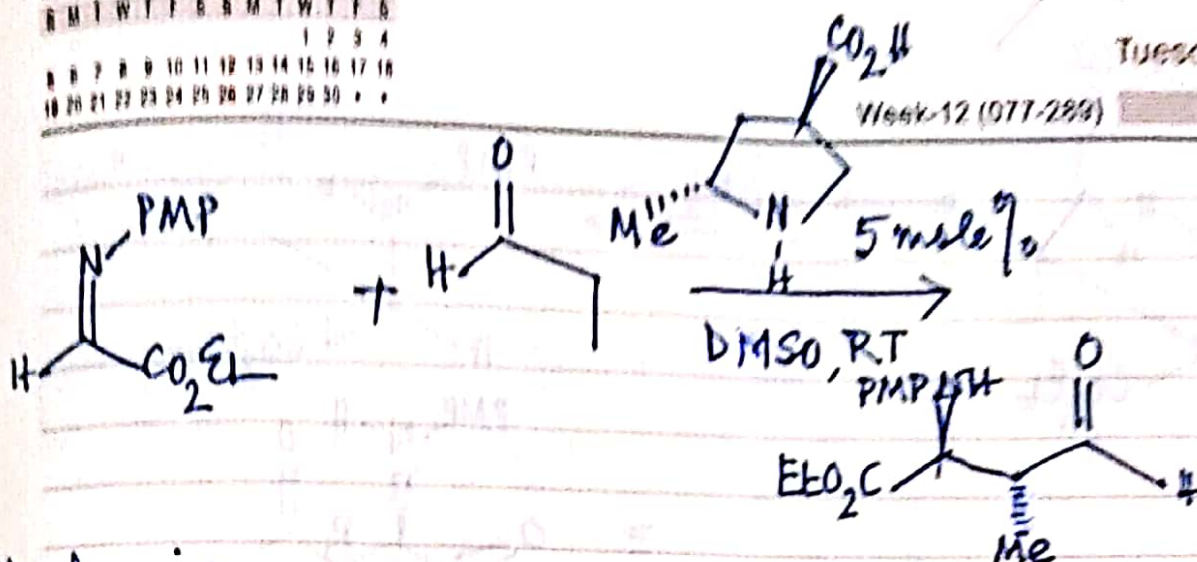
2020

S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
								1	2	3	4	5	6	7
8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
23	24	25	26	27	28	29	30	31						

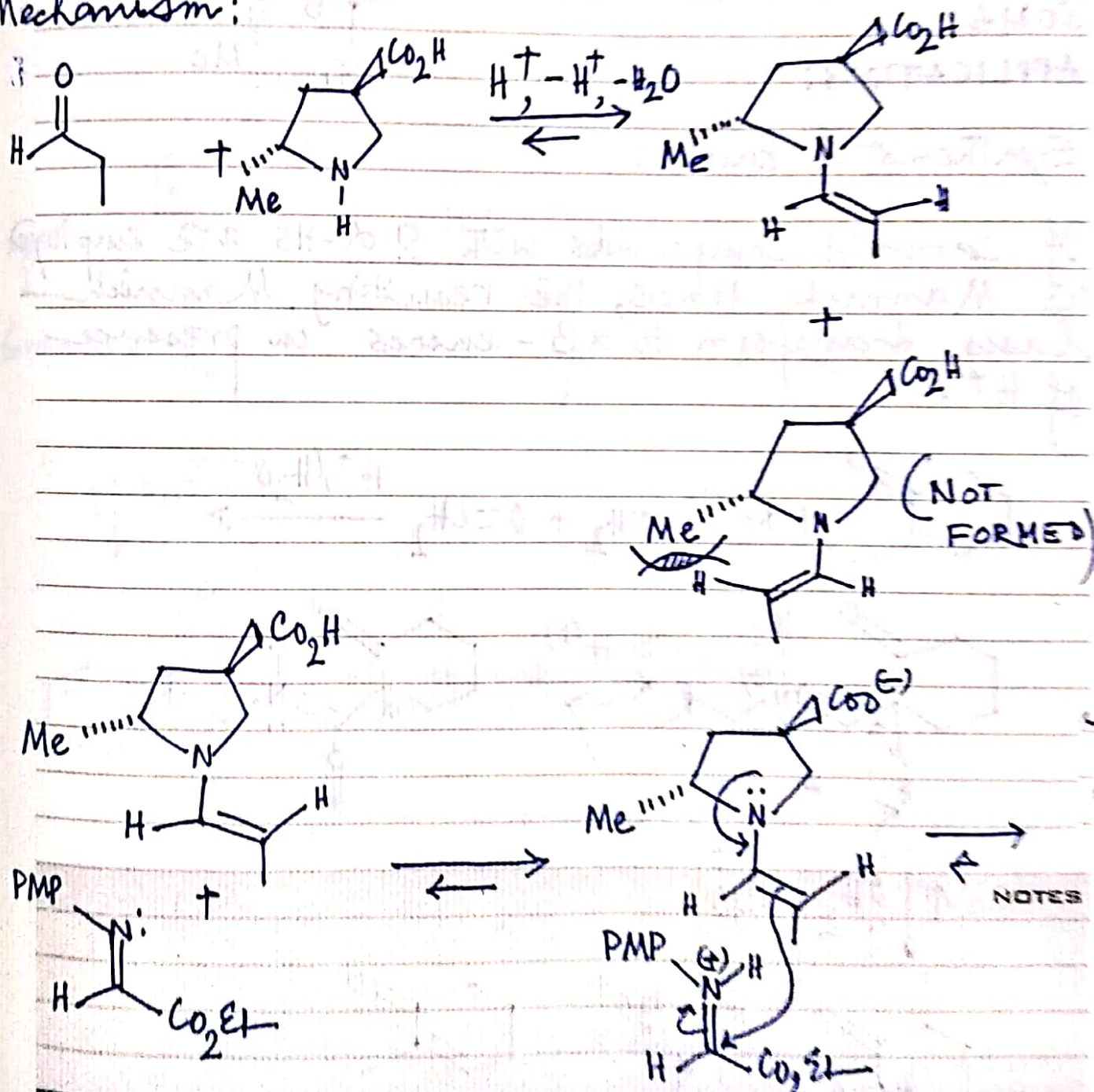


NOTES

You may find the worst enemy or best friend in yourself. – English Proverb



Mechanism:



18

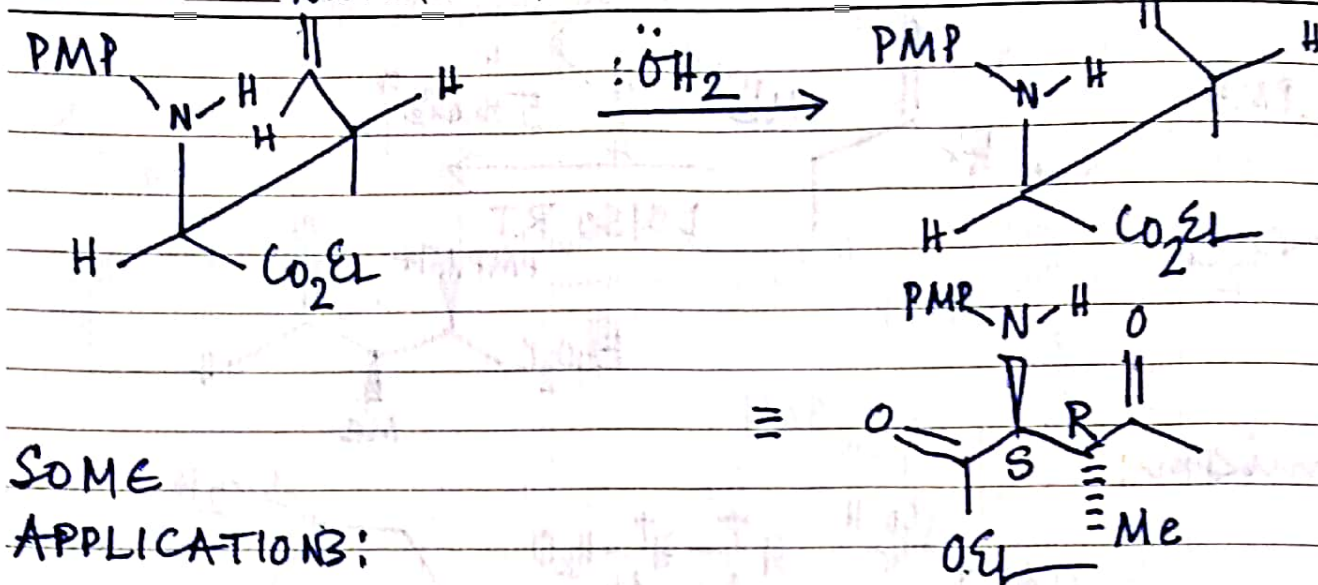
Wednesday

Mar 2020 Week-12 (078-288)

March

2020

S	M	T	W	T	F	S	S	M	T	W	T	F	S
						1	2	3	4	5	6	7	
8	9	10	11	12	13	14	15	16	17	18	19	20	21
22	23	24	25	26	27	28	29	30	31	•	•	•	•

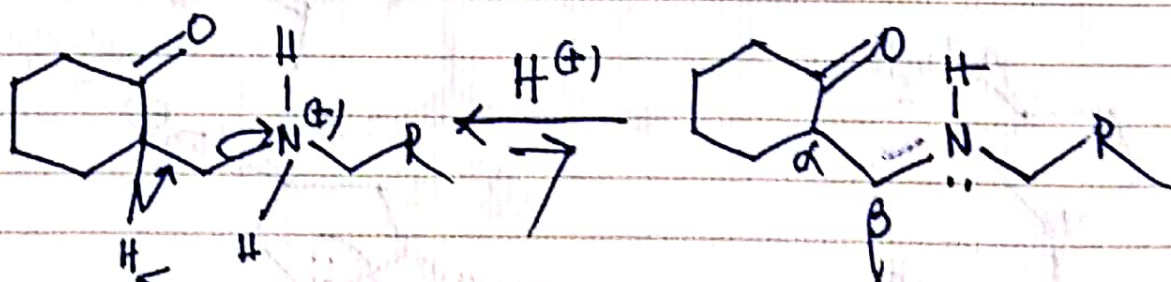
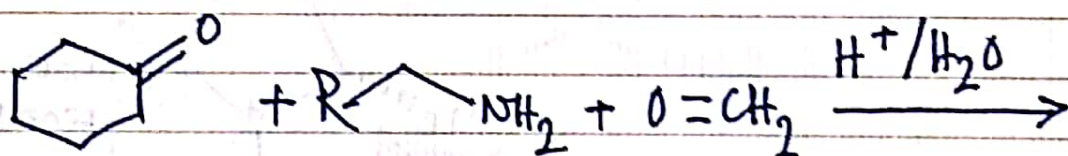


SOME

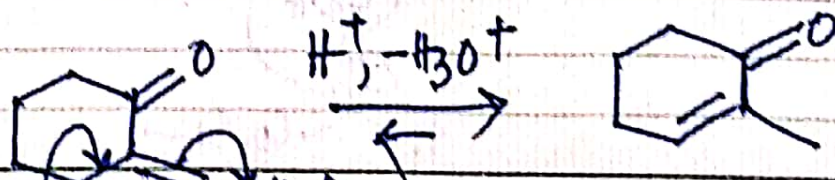
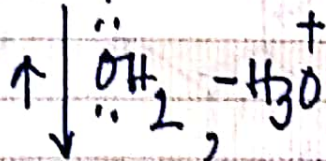
APPLICATIONS:

Synthesis of Enones:

If carbonyl compounds with 2 α -Hs are employed as Mannich donors, the resulting Mannich bases transform to $\alpha\beta$ -enones in presence of H^+ .

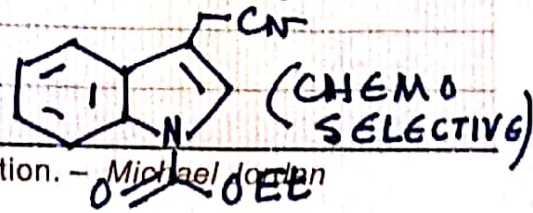
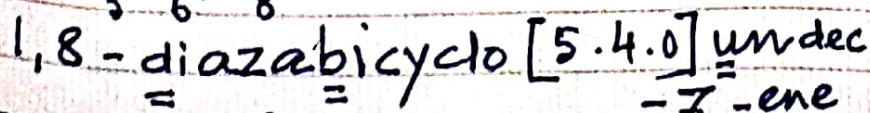
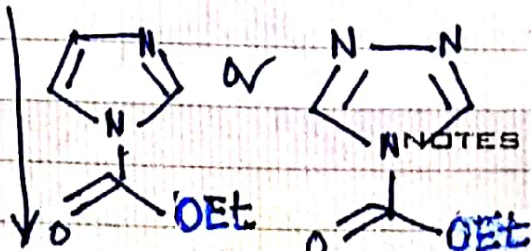
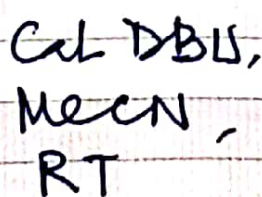
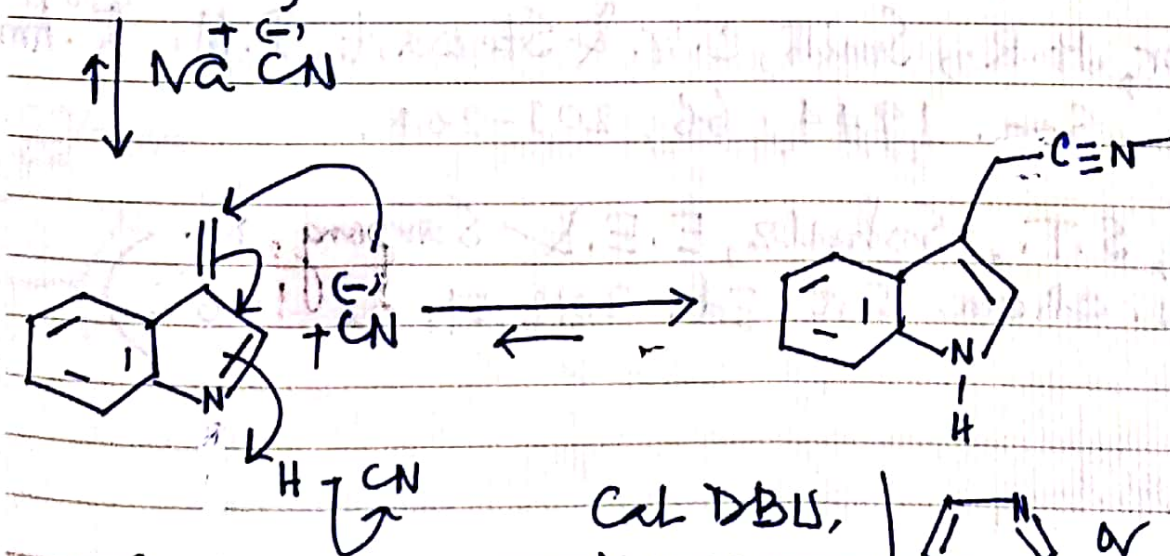
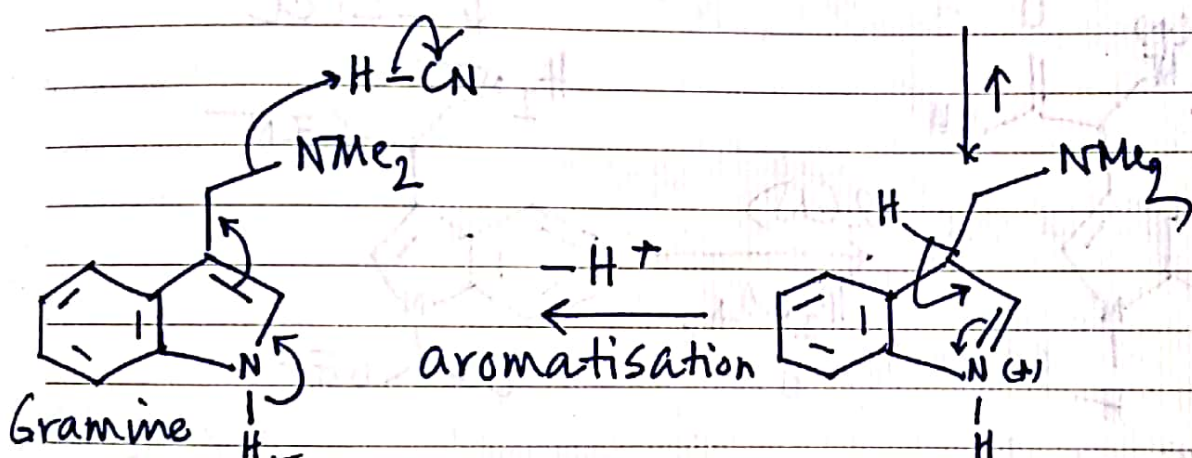
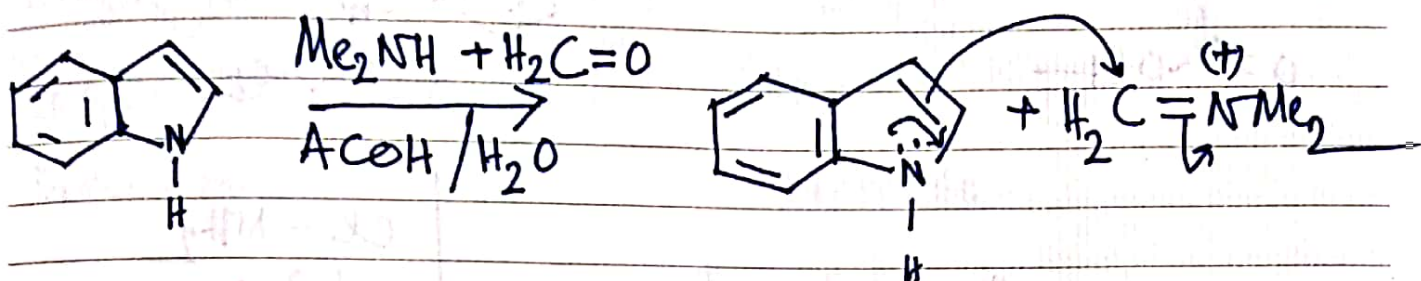


NOTES



It makes a big difference in your life when you stay positive. - Ellen DeGeneres

Synthesis of Gramine, Tryptophan:



Always turn a negative situation into a positive situation. - Michael Jordan

20

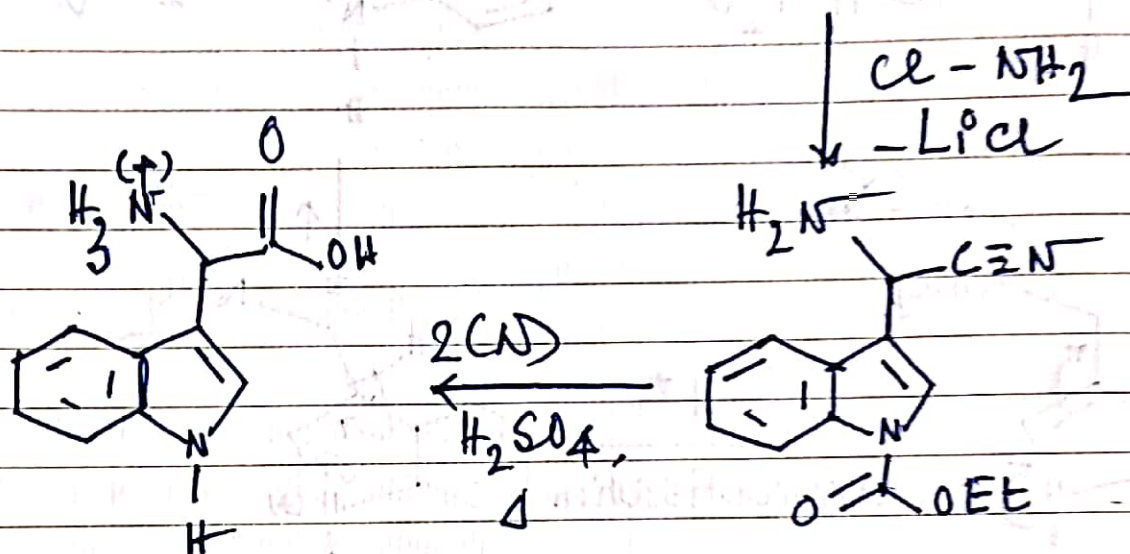
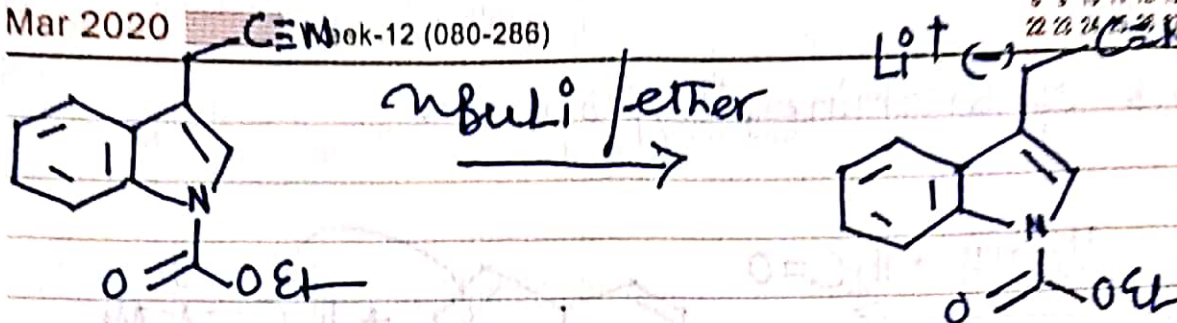
Friday

Mar 2020

CEN Book-12 (080-286)

March

S	M	T	W	T	F	S	S	M	T	W	T	F	S
							1	2	3	4	5	6	7
8	9	10	11	12	13	14	15	16	17	18	19	20	21
22	23	24	25	26	27	28	29	30	31	...	...	...	...



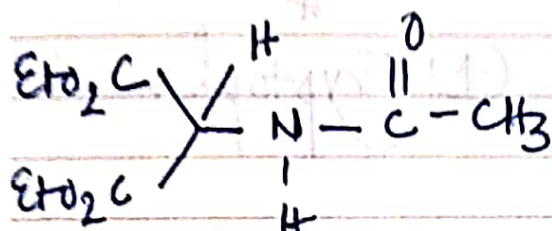
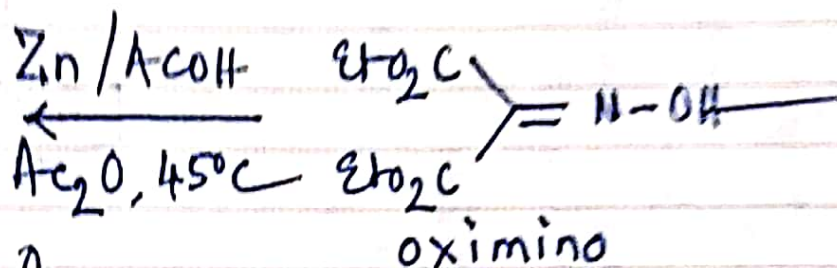
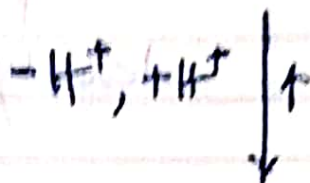
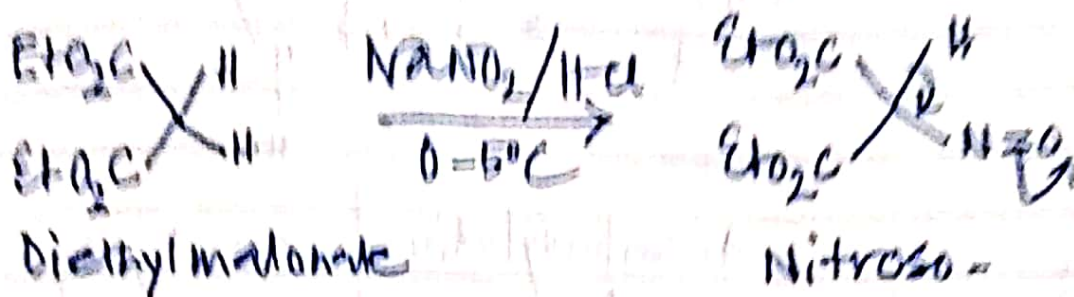
(+) Tryptophan

(Snyder, H.R., Smith, C.W. & Stewart, J.M. J. Am. Chem. Soc. 1944, 66, 200-204.

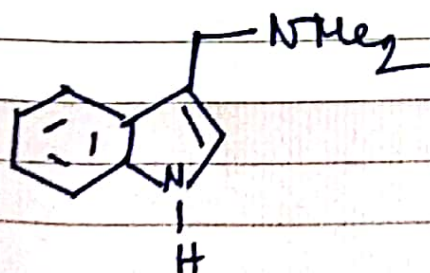
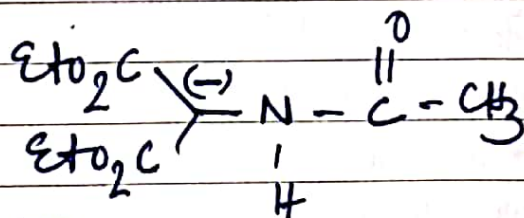
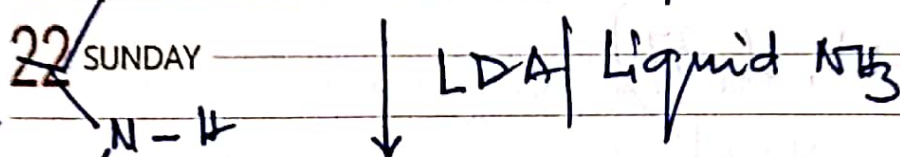
Heller, S.T., Schulz, E.E. & Sarpong, R. Angew. chem. Int. Ed. 2012, 51, 11-6.)

NOTES

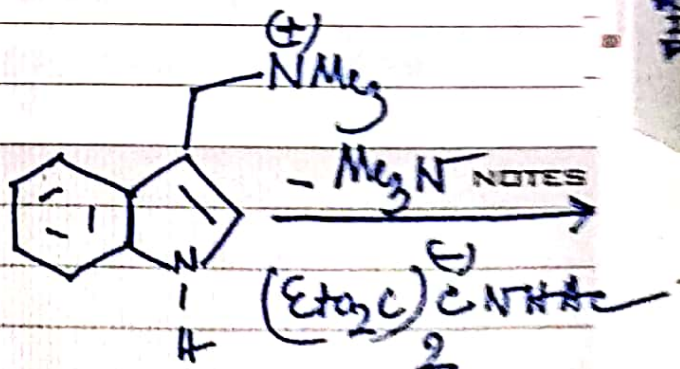
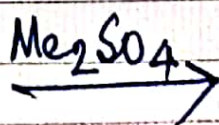
Albertson, N. F., et al.



Acetamido diethyl malonate



Gramine

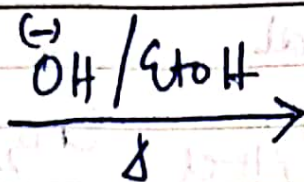
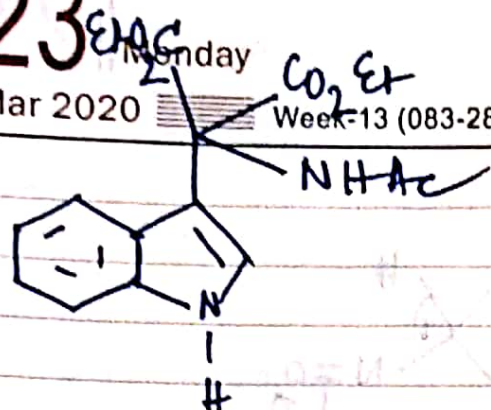


23

Monday

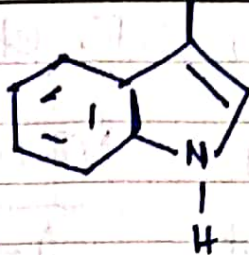
Mar 2020

Week-13 (083-283)



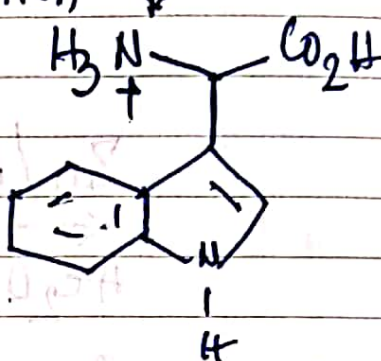
March 2020

S	M	T	W	T	F	S
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				



decarboxylation

deacetylation

2(N) H_2SO_4 

(+)-Tryptophan

(Albertson, N.F., Archer, S.

& Suter, C.M. I. Am. Chem.

Soc. 1945, 67:1, 36-37)

2020

April

S M T W T F S S M T W T F S

1 2 3 4

5 6 7 8 9 10 11 12 13 14 15 16 17 18

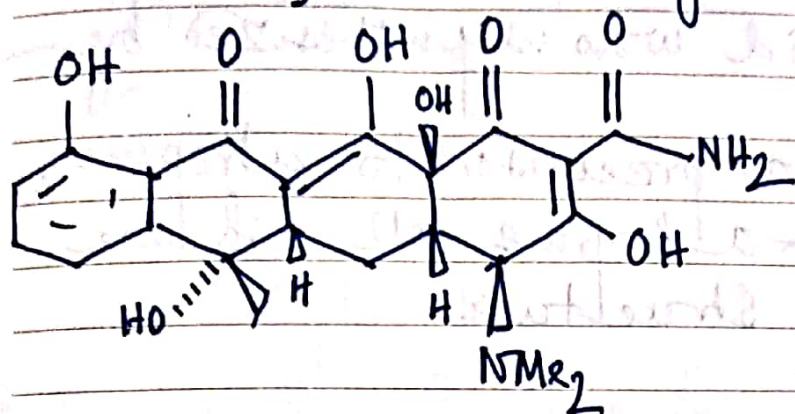
19 20 21 22 23 24 25 26 27 28 29 30 • •

Tuesday

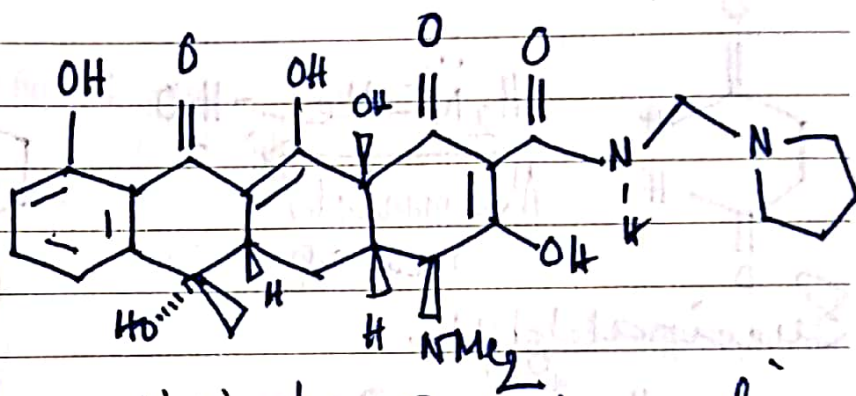
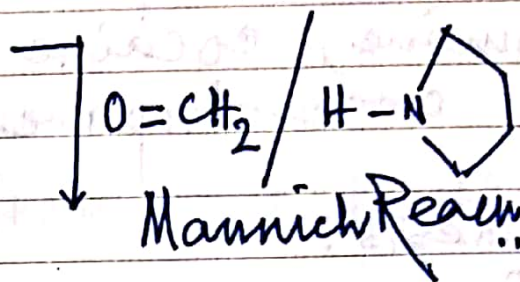
24

Week-13 (084-282) Mar 2020

Synthesis of Rolitetracycline:



Tetracycline



Pyrrolidinylmethyltetracycline
(Rolitetracycline)

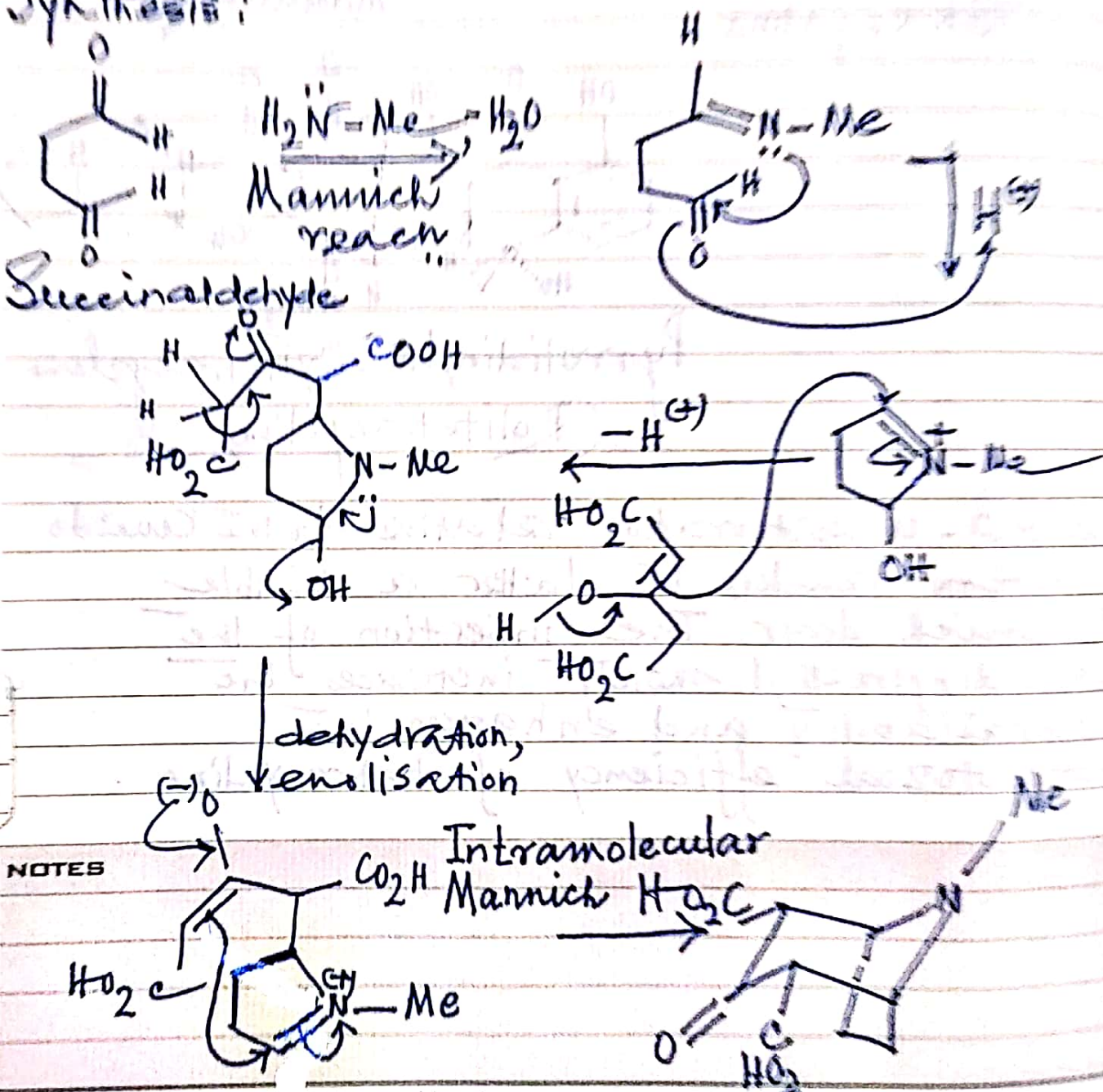
The α, β -unsaturation relative to the amide function renders the latter a viable Mannich donor. The insertion of the pyrrolidinylmethyl moiety increases the bioavailability and enhances the antiprotozoal efficiency of tetracycline.

NOTES

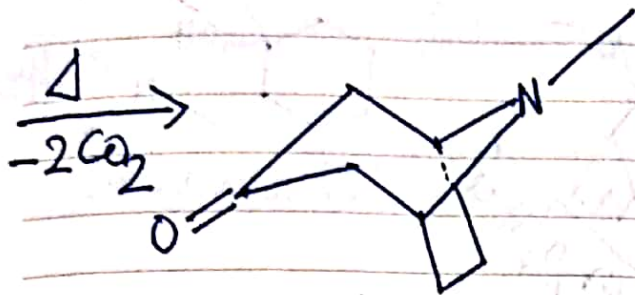
Synthesis of Tropicone!

Tropicone, an alkaloid was synthesized by Robinson in 1917 as a precursor to atropine. Tropicone, cocaine & tropine all share the core tropane structure.

Synthesis:



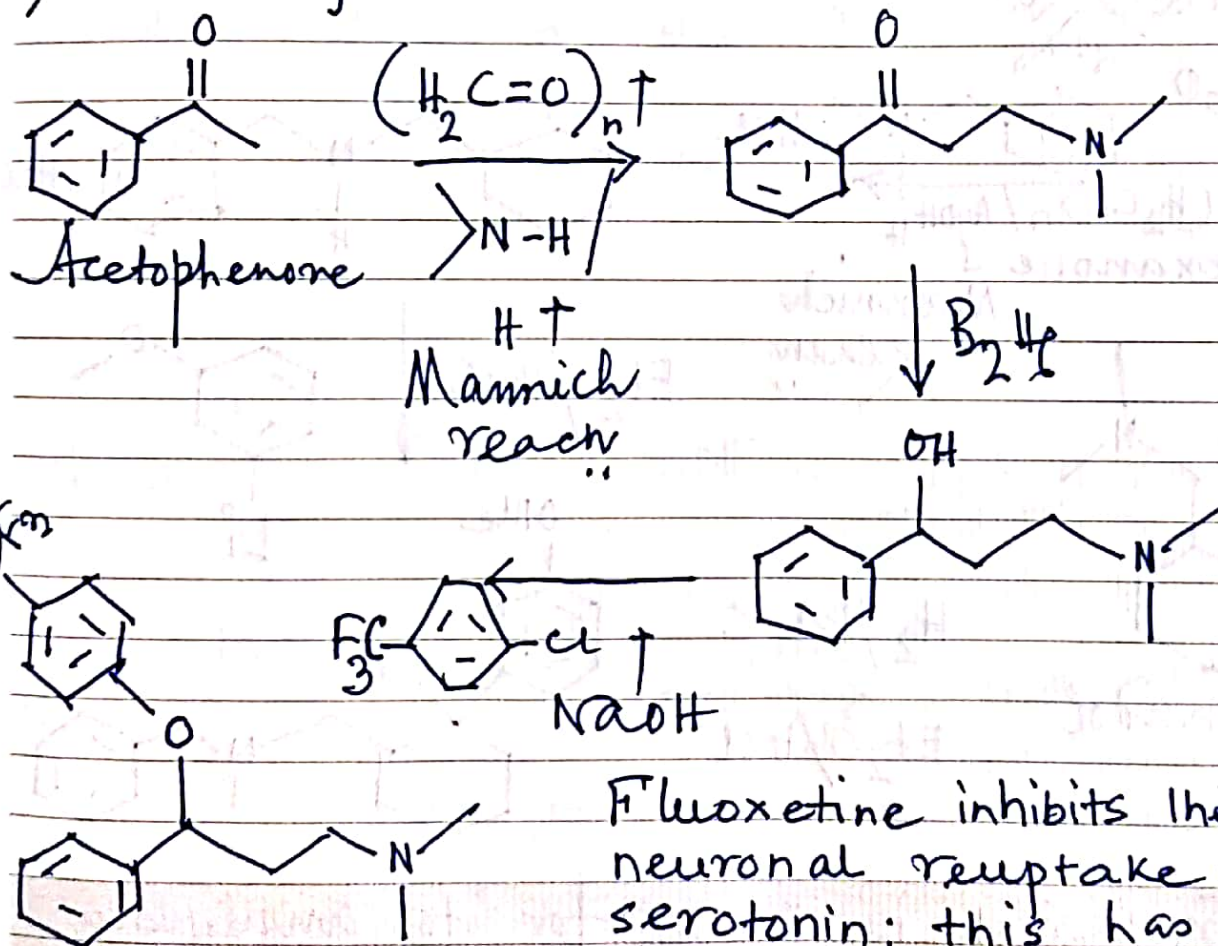
NOTES



Troponone

(Robinson, R. J. Chem. Soc., Trans. 1917, III, 762-768)

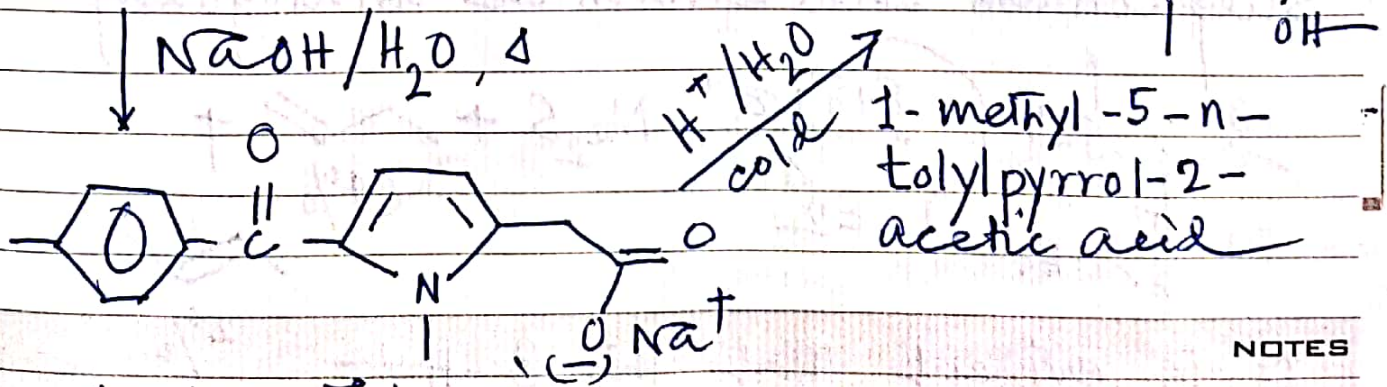
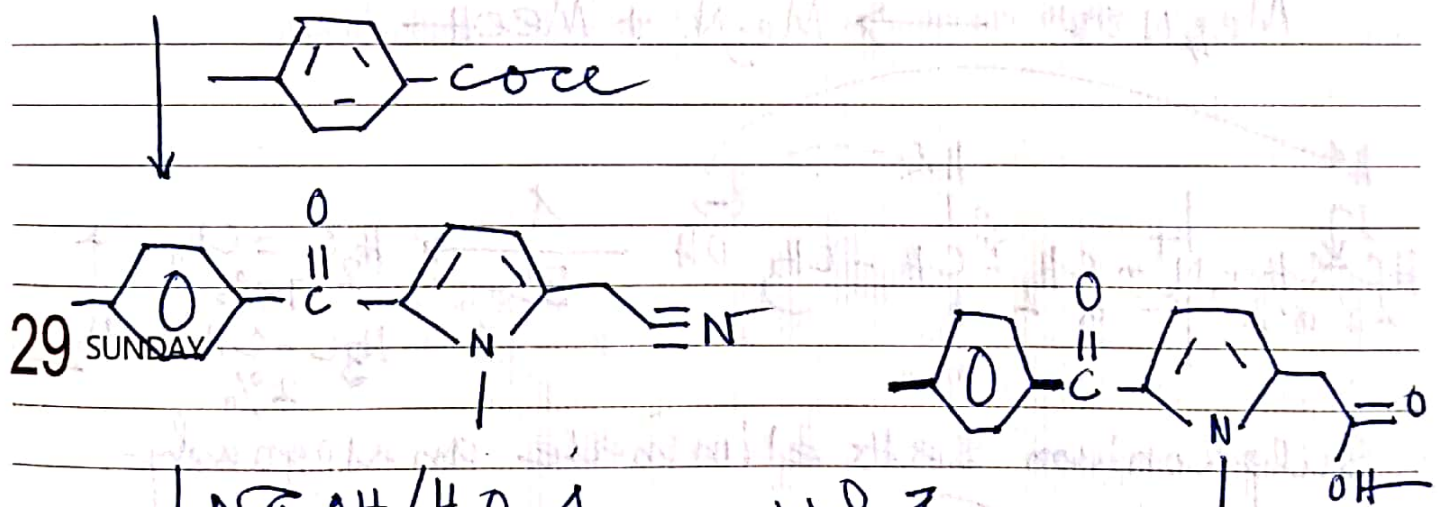
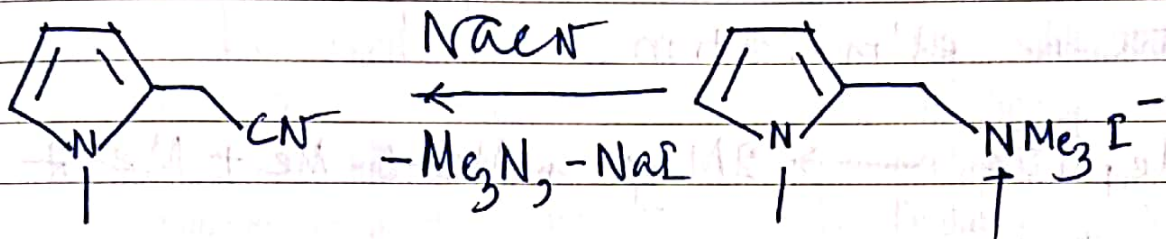
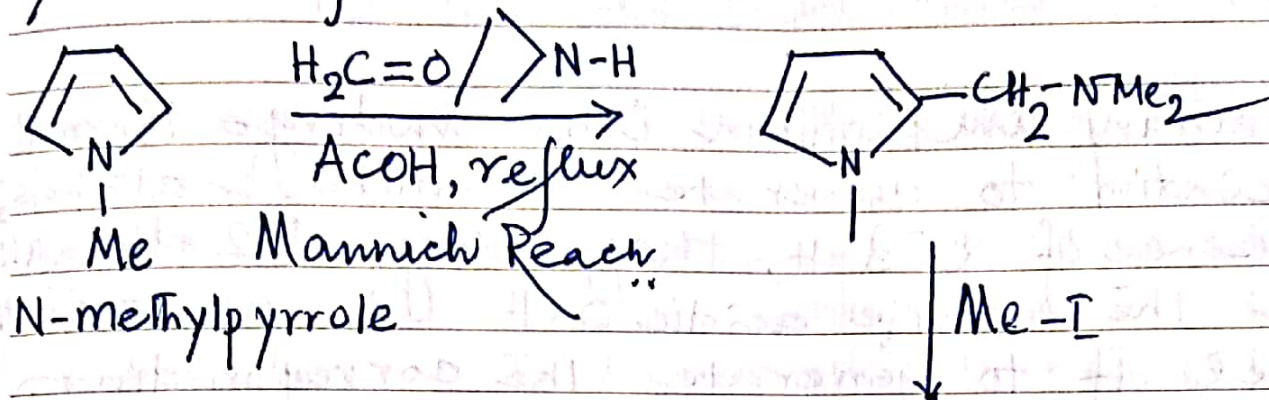
Synthesis of Fluoxetine:



(±) Fluoxetine

Fluoxetine inhibits the neuronal reuptake of serotonin; this has a direct relation on its antidepressant activity.

Synthesis of Tolmetin:



Sodium Tolmetin

Tolmetin is a non steroidal anti-inflammatory agent and acts by reducing prostaglandin synthesis.